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49. (Amended) The method of claim 41, wherein the method ameliorates the symptoms of age-related macular degeneration.

REMARKS

Claims 5, 36, 37, 44 and 46 have been cancelled. Claims 1, 6, 8, 32, 33, 38, 40, 41, 45 and 49 have been amended. Upon entry of this paper, claims 1-4, 6, 8, 9, 32-35, 38-43, 45, and 47-49 will be pending in this application.

Support for the amendments may be found throughout the application as filed. Support for the amendments to claims 1, 33 and 41 may be found, for example, on page 16, lines 19-20, and page 9, line 12 of the application as filed. Support for the amendments to claims 6, 38 and 45 may be found, for example, on page 9, lines 15-16 of the application as filed. Support for the amendments to claim 8 may be found, for example, in Example 1 as filed. Support for the amendments to claims 32, 40, and 49 may be found, for example, on page 23, line 7 as filed. Applicants believe that the amendments introduce no new matter.

According to section 5 of the outstanding Office Action, it appears that the Office has not considered the art cited in Applicants PTO-1449 form, mailed April 25, 2002. The Office indicated that it had not received the cited art. Applicants enclose copies of the April 25, 2002 Information Disclosure Statement, PTO-1449 form, and copies of the art cited thereon, and request that the Examiner confirm that the cited art has been considered by initialing each citation, and then signing and dating each page of the PTO-1449 form. In addition, Applicants enclose a Supplemental Information Disclosure Statement, PTO-1449 form, and copies of the art cited thereon for consideration by the Examiner. Applicants request that the Examiner confirm that the cited art has been considered by initialing each citation, and then signing and dating each page of the PTO-1449 form.

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Rejection Under 35 U.S.C. §112, First Paragraph - Enablement

According to sections 6 and 7 of the outstanding Office Action, claims 1-6, 8-9, and 32-49 presently stand rejected under 35 U.S.C. §112, first paragraph for lack of enablement. Applicants respectfully traverse this rejection to the extent that it is maintained over the claims, as amended, and request that the rejection be reconsidered and withdrawn.

The test for enablement is whether persons skilled in the art can make and use the invention without undue experimentation (see, MPEP 2164.01; see also, MPEP 2164.02). Applicants submit that the claimed method has been amended to require the use of a specific anti-angiogenesis factor (for example, angiostatin and an anti-vascular endothelial growth factor antibody) and a certain class of photosensitizer (for example, a tetrapyrrole derivative photosensitizer). Applicants submit that the claims, as amended, are not unduly broad and that a skilled artisan in possession of Applicants' disclosure would be fully enabled to practice the claimed methods of treating unwanted choroidal neovasculature (CNV) without undue experimentation.

As stated in the Office Action, the courts have identified several factors for assessing whether a disclosure requires undue experimentation. These factors include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance provided, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the art, and (8) the breadth of the claims. *In re Wands*, 8 USPQ2d 1400 (CAFC 1988). Applicants respectfully submit that, under the *Wands* test, the specification enables one of ordinary skill in the art to practice the claimed invention without undue experimentation. Each of the *Wands* factors are discussed in more detail below.

Nature of the Invention and Breadth of the Claims

The present invention is directed to a photodynamic therapy (PDT)-based method of treating unwanted CNV comprising endothelial cells in a mammal. Independent claims 1, 33 and 41 all require the steps of: (a) administering to the mammal an anti-angiogenesis factor selected

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from the group consisting of angiostatin and an anti-vascular endothelial growth factor antibody in an amount sufficient to permit an effective amount to localize in the CNV; (b) administering to the mammal an amount of a tetrapyrrole derivative photosensitizer sufficient to permit an effective amount to localize in the CNV; and (c) irradiating the CNV with laser light to activate the photosensitizer, wherein the activated photosensitizer induces damage to the CNV resulting in its occlusion.

State of the Prior Art, and Relative Skill of Those in the Art

Applicants submit that, at the time the invention was made, the state of the art was advanced and the level of skill in the art was high.

The art cited in the specification, cited on the PTO-1449 forms of record, or applied by the Examiner, all show the advanced state of the art. For example, U.S. Patent No. 5,707,986 (already of record) shows that, prior to the filing of the instant application, it had been possible to selectively occlude CNV in primate eyes using green porphyrin-based PDT. Furthermore, the disclosures in the art of record evidence the fact that, as found in *Wands*, “[t]here was a high level of skill in the art at the time the application was filed.” 8 USPQ2d at 1406.

Amount of Direction or Guidance Provided, and the Quantity of Experimentation

Applicants have provided extensive guidance regarding the practice of the invention. The specification provides a detailed discussion with respect to the choice of an appropriate angiogenesis factor, its dosage and its mode of administration, the choice of an appropriate photosensitizer, its dosage and its mode of administration, and the irradiation conditions (for example, the time between dye administration and light activation, the fluence, the irradiance, and the wavelength of the laser light) to activate the photosensitizer.

For example, with respect to the photosensitizer, page 9, lines 12-29 of the specification discuss exemplary tetrapyrrole derivative photosensitizers useful in the practice of the invention, and direct the artisan to particular citations for further information concerning those photosensitizers. Furthermore, the specification provides a detailed discussion of suitable formulations for the photosensitizer (see page 10, lines 16 through page 11, line 11 of the

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application as filed), dosages of the photosensitizer (see page 13, lines 13-18 of the application as filed), and modes of administration of the photosensitizer (see page 13, lines 1-6 of the application as filed).

In addition, with regard to the irradiation parameters, the specification provides a detailed discussion of the optimal wavelength values for the laser light (see, for example, page 13, lines 19-27 of the application as filed), the choice of appropriate irradiance values (see, for example, page 14, lines 8-13 of the application as filed), the choice of appropriate fluence values (see, for example, page 14, lines 5-8 of the application as filed) and the timing of irradiation after administration of the photosensitizer (see, for example, page 4, lines 14-30 of the application as filed). In addition, the specification discusses methods for monitoring the efficacy of photodynamic therapy (see, for example, page 15, lines 1-7 of the application as filed).

With regard to an anti-angiogenesis factor useful in the practice of the invention, the claims as amended now require angiostatin and/or an anti-vascular endothelial growth factor antibody. These anti-angiogenesis factors are described on page 16 of the application as filed. The specification provides a detailed description of the dosages (see, for example, page 18, line 26 through page 19, line 4 of the application as filed) and modes of administration (see, for example, page 19, lines 5-16 of the application as filed) of these anti-angiogenesis factors.

Working Examples

Applicants respectfully submit that the courts have long held that "there is no magical relationship between the number of representative examples and the breadth of the claims; the number and variety of examples are irrelevant if the disclosure is 'enabling' and sets forth the 'best mode contemplated.'" *In re Borkowski*, 422 F.2d 904, 910, 164 USPQ 642 (CCPA 1970).

Notwithstanding the foregoing, Applicants submit that the specification provides specific working examples. By way of example, Example 1, appearing on pages 23-26 of the specification describes a PDT protocol using the tetrapyrrole derivative photosensitizer, Lu-Tex, in combination with the anti-angiogenesis factor, angiostatin. The Example describes the type of protocol that may be used *in vivo*.

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The Office Action on page 6, however, states that, "the specification does not teach how to extrapolate data obtained from *in vitro* proliferation and apoptosis assays to the development of effective *in vivo* human therapeutic compositions as a method of treating unwanted choroidal neovasculature." Applicants submit that the specification provides adequate guidance to those skilled in the art on how to provide an effective treatment *in vivo*. Example 1, for example, teaches that the tetrapyrrole derivative photosensitizer Lu-Tex and the anti-angiogenesis factor, angiostatin, when combined, can have a synergistic cytotoxic effect on retinal capillary endothelial cells. The *in vitro* assay provides information regarding appropriate dosages and light levels.

Furthermore, Applicants refer the Examiner to a copy of an abstract (citation C115 in the enclosed Supplemental Information Disclosure Statement), the substance of which is scheduled to be presented in May of 2003 at the Annual Meeting of the Association of Research in Vision and Ophthalmology in Fort Lauderdale, Florida. The abstract discusses a series of experiments performed in accordance with the teachings of the specification that demonstrate that a PDT protocol for the treatment of CNV *in vivo* may be more effective if the recipient is pre-treated with an anti-angiogenesis factor. The results demonstrate that, at the dosages of angiostatin used in these experiments, angiostatin alone did not prevent the development of CNV. However, continuous administration of angiostatin prior to PDT using the tetrapyrrole derivative Verteporfin significantly reduced the development of CNV relative to PDT alone.

In addition, Applicants refer the Examiner to citation C101 in the enclosed Supplemental Information Disclosure Statement, which is a summary of the Jules Gonin Lecture given by Dr. Joan W. Miller (a co-inventor of the claimed subject matter) to the Macula Society in September 2002 at the time she received the Club Jules Gonin Retina Research Award from the Club Jules Gonin. The third and fourth pages, for example, of the article summarize *in vivo* experiments combining PDT using Verteporfin with the anti-angiogenesis factor, anti-vascular endothelial growth factor antibody (RhuFab V2). The fourth paragraph on page four states that, "preclinical results show that RhuFab V2 intravitreal injection plus Verteporfin PDT is safe and appears to result in a greater reduction in angiographic leakage from CNV than PDT alone."

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Predictability of the Art

Notwithstanding the assertion in the Office Action that the "pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity," Applicants submit that the specification provides adequate guidance to those skilled in the art commensurate with the scope of the claims. Moreover, as described above, the specification itself provides the skilled artisan with significant guidance with respect to each of the components necessary to practice the invention. Thus, in accordance with the legal standard set forth in *Wands*, and for the sake of argument even if the art were to be held to be unpredictable, the skilled artisan in possession of Applicants' application would be enabled to practice the invention without undue experimentation.

In summary, Applicants respectfully submit that the specification is sufficient to enable one of ordinary skill in the art to practice the claimed invention without undue experimentation, and that the claims fully comply with all the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection Under 35 U.S.C. §112, First Paragraph – Written Description

According to sections 6 and 8 of the outstanding Office Action, claims 1-6, 8-9, and 32-49 presently stand rejected under 35 U.S.C. §112, first paragraph for lack of written description. Applicants respectfully traverse this rejection to the extent that it is maintained over the claims, as amended.

In view of the amendments to the claims, the previous discussion with regard to enablement, together with the scope and content of the articles discussed therein, Applicants submit that the Applicants clearly were in possession of the invention at the time the application was filed. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

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Rejections Under 35 U.S.C. §103(a)

According to sections 9, 10, and 11 of the outstanding Office Action, claims 1-6, and 32-49 presently stand rejected under 35 U.S.C. §103(a) over U.S. Patent No. 6,162,242 (the ““242 Patent”) in view of U.S. Patent No. 5,733,876 (the ““876 Patent”). Applicants respectfully traverse this rejection to the extent that it is maintained over the claims, as amended, and respectfully request that this rejection be reconsidered and withdrawn.

Applicants’ claimed invention is directed to a method of treating unwanted choroidal neovasculature comprising endothelial cells. The method comprises (i) administering to a mammal in need of such treatment an anti-angiogenesis factor (for example, angiostatin or an anti-vascular endothelial growth factor receptor antibody), (ii) administering to the mammal a tetrapyrrole derivative photosensitizer, and (iii) irradiating the CNV so as to activate the photosensitizer which then causes occlusion of the CNV.

35 U.S.C. §103 states that the subject matter, taken as a whole, must be considered when evaluating the patentability of an invention under 35 U.S.C. §103. The case law on this is quite clear. In addition, the consistent criteria for the determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that the claimed subject matter should be carried out, and would have a reasonable likelihood of success. Both the suggestion and the expectation of success must be founded in the prior art, not in Applicant's disclosure. *In re Dow Chemical Company*, 5 USPQ2d 1529, 1530 (Fed. Cir. 1988).

Furthermore, the case law is clear where references are combined. In order for a combination of references to render an invention obvious, it must be obvious that their teachings can be combined. That is, obviousness cannot be established by combining the teachings of the prior art to produce claimed invention, absent some teaching, suggestion or incentive in the art supporting the combination. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). Citing references which merely indicate the isolated elements recited in the claims is not a sufficient basis for concluding that the combination would have been obvious. *Ex parte Hiyamaizu*, 10 USPQ2d 1393 (BPAI 1988). Applicants submit, for the reasons set forth below, that nothing in any of the

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references suggest their combination, and nothing in any of the references lays the foundation for a reasonable expectation of success, were such a combination to be made.

The '242 Patent discloses a method of performing PDT. The method involves (i) administering a photosensitizer, (ii) allowing sufficient time for the photosensitizer to be released from abnormal blood vessels into a site adjacent the abnormal vessel while maintaining the photosensitizer within normal blood vessels, (iii) transiently constricting the normal vessels to displace the photosensitizer out of the normal vessels, (iv) phototreating the site to treat the abnormal vessel having photosensitizer in the adjacent tissue, and (v) restoring the normal vessels to an unstricted state. According to the '242 Patent, the method may also include the use of, for example, a vessel occluding agent, for example, adenosine diphosphate. The '242 Patent, however, does not teach or suggest combining the PDT method with an anti-angiogenesis factor.

The '876 Patent discloses using angiostatin to inhibit angiogenesis and to inhibit endothelial cell proliferation. The '876 Patent, however, fails to teach or suggest the including angiostatin in a PDT method for treating unwanted CNV.

At the outset, Applicants submit that there is no teaching or suggestion whatsoever in any of the applied references that would motivate the skilled artisan to "substitute the coagulation factor" in the '242 Patent with angiostatin as taught in the '876 Patent. Furthermore, Applicants submit that, even if such a combination were to be made, the skilled artisan would have no reasonable expectation that such a method would be effective at occluding CNV.

Applicants submit that agents that promote the formation of thrombi or clots as discussed in the '242 Patent (for example, adenosine diphosphate) are completely different (both in structure and function) to angiostatin as discussed in the '876 Patent. The occluding agent of the '242 Patent occludes blood vessels, for example, by promoting blood clot formation. In contrast, angiostatin as discussed in the '876 Patent blocks the growth of new blood vessels. Applicants submit that these are two completely different physiological effects. Applicants submit that there is no reason for the skilled artisan to believe that an anti-angiogenesis agent, which acts to inhibit

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the growth of new blood vessels, would be useful at occluding already existing blood vessels, as required by the teachings of the '242 Patent.

Furthermore, there is no teaching or suggestion in the applied references that would provide the skilled artisan with a reasonable expectation that a PDT-based method, when combined with an anti-angiogenesis factor, would be effective in treating CNV. Applicants submit that the motivation to practice the claimed invention coupled with the reasonable expectation of success articulated in the Office Action represents impermissible hindsight reconstruction of the claimed invention, which would not have been possible without the benefit of the Applicants' disclosure. The courts have held that one cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.

In re Fine, 5 USPQ2d at 1600.

Moreover, there is nothing that would suggest that the combined method would be more effective than the sum of each of the separate treatments of PDT and the administration of anti-angiogenesis factor. These unexpected findings are shown in both the application as filed and in citation C115, enclosed. Citation C115, for example, discloses *in vivo* experiments which demonstrate that angiostatin can potentiate the efficacy of Verteporfin PDT to close CNV. At the doses used in these experiments, angiostatin alone did not prevent the growth of CNV. In contrast, continuous pretreatment with angiostatin potentiated significantly the efficacy of Verteporfin PDT for CNV closure relative to a PDT alone. For example, when PDT alone was conducted using a fluence of 10J/cm^2 , about 40% of the lesions lacked angiographic leakage. In contrast, when the PDT was conducted following continuous administration of angiostatin, at least about 90% of the lesions lacked angiographic leakage. Applicants submit that these synergistic results could not have been predicted based on the teachings of the applied references. Accordingly, Applicants submit that, even if the skilled artisan were motivated to combine the teachings of the '242 Patent with those of the '876 Patent, the skilled artisan would have no reasonable expectation that the claimed method would be so effective at closing unwanted CNV.

In view of the foregoing, Applicants respectfully submit that the claimed invention would not have been obvious to those skilled in the art at the time the invention was made, and

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respectfully request that the rejection based on the '242 Patent and the '876 Patent be reconsidered and withdrawn.

According to sections 9, 10 and 12 of the outstanding Office Action, claims 1-6, and 32-49 presently stand rejected under 35 U.S.C. §103(a) over either U.S. Patent No. 5,707,986 (the "986 Patent") or U.S. Patent No. 6,270,749 (the "749 Patent") in view of the '876 Patent. Applicants respectfully traverse this rejection to the extent that it is maintained over the claims, as amended, and respectfully request that this rejection be reconsidered and withdrawn.

Applicants respectfully submit that, for the reasons set forth below, there is no teaching or suggestion in any of the applied references that suggest their combination, and that nothing in any of the references lays the foundation for a reasonable expectation of success, were such a combination to be made. Applicants further submit that the claimed invention has unexpected properties that would not have been foreseeable by the skilled artisan at the time the invention was made.

The '986 Patent discloses a PDT method employing a green porphyrin dye for the treatment of unwanted CNV. The '749 Patent discloses a PDT method employing a texaphyrin dye for the treatment of CNV. Neither the '986 Patent nor the '749 Patent teach, suggest or infer combining their respective PDT methods with an anti-angiogenesis factor.

The '876 Patent, as discussed above, discloses using angiostatin to inhibit angiogenesis and to inhibit endothelial cell proliferation. The '876 Patent fails to teach, suggest or even infer including angiostatin in a PDT-based method for treating unwanted CNV.

For reasons analogous to those discussed previously, Applicants submit that there is nothing in any of the applied references that would motivate the skilled artisan to combine the teachings of the '986 Patent or the '749 Patent with those of the '876 Patent. For sake of argument only, even if the teachings were combined as suggested in the Office Action, Applicants submit that the skilled artisan would not reasonably expect that the method would be so effective at closing unwanted CNV. As discussed before, Applicants submit that the motivation to practice the claimed invention coupled with the reasonable expectation of success

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articulated in the Office Action represents impermissible hindsight reconstruction of the claimed invention, which would not have been possible without the benefit of the Applicants' disclosure.

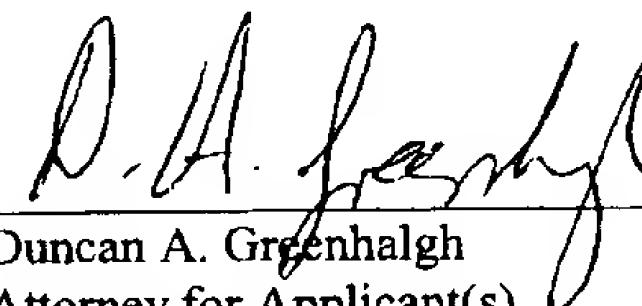
Furthermore, for the reasons discussed above with regard to citation C115, Applicants submit that the skilled artisan would have no reason to believe that the combined method would be so effective at closing unwanted CNV.

In view of the foregoing, Applicants respectfully submit that the claimed invention would not have been obvious to the skilled artisan relying on the teachings of the '986 Patent, the '749 Patent and the '876 Patent, either alone or in combination, and respectfully request that this rejection be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing, Applicants respectfully submit that the case is in condition for immediate allowance. Early favorable action is respectfully solicited.

Respectfully submitted,



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MARKED-UP COPY OF THE AMENDED CLAIMS

1. (Twice Amended) A method of treating unwanted choroidal neovasculature comprising endothelial cells in a mammal, the method comprising the steps of:
 - (a) administering to the mammal an anti-angiogenesis factor selected from the group consisting of angiostatin and an anti-vascular endothelial growth factor antibody, endostatin, a peptide containing a RGD tripeptide sequence that binds α_vβ₃ integrin, an antibody that binds α_vβ₃ integrin, a COX 2 inhibitor, a molecule that binds vascular endothelial growth factor receptor, a molecule that binds epidermal growth factor receptor, a molecule that binds vascular endothelial growth factor, a tyrosine kinase inhibitor, and a pigment epithelium derived growth factor,] in an amount sufficient to permit an effective amount to localize in the choroidal neovasculature;
 - (b) administering to the mammal an amount of a tetrapyrrole derivative photosensitizer sufficient to permit an effective amount to localize in the choroidal neovasculature; and
 - (c) irradiating the choroidal neovasculature with laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal neovasculature, wherein damage to the endothelial cells resulting from steps (a), (b), and (c) is greater than that resulting only from steps (b) and (c).
6. (Amended) The method of claim [§] 1, wherein the photosensitizer is lutetium texaphyrin, [a] benzoporphyrin, [a] benzoporphyrin derivative, [a] hematoporphyrin, or [a] hematoporphyrin derivative.
8. (Amended) The method of claim 1, wherein occlusion of the choroidal neovasculature resulting from the combination of steps (a), (b) and (c) is greater than that resulting from the sum of steps (a), (b) and (c) alone.

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32. (Amended) The method of claim 1, wherein the method ameliorates the symptoms of [a disorder selected from the group consisting of] age-related macular degeneration[, ocular histoplasmosis syndrome, pathologic myopia, angioid streaks, idiopathic disorders, choroiditis, choroidal rupture, overlying choroid nevi, and inflammatory diseases].
33. (Amended) A method of treating unwanted choroidal neovasculature comprising endothelial cells in a mammal, the method comprising the steps of:
 - (a) administering to the mammal an anti-angiogenesis factor selected from the group consisting of angiostatin and an anti-vascular endothelial growth factor antibody in an amount sufficient to permit an effective amount to localize in the choroidal neovasculature;
 - (b) administering to the mammal an amount of a tetrapyrrole derivative photosensitizer sufficient to permit an effective amount to localize in the choroidal neovasculature; and
 - (c) irradiating the choroidal neovasculature with laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal neovasculature, wherein the occlusion caused by step (a) is synergistic with the occlusion caused by steps (b) and (c).
38. (Amended) The method of claim [37] 33, wherein the photosensitizer is lutetium texaphyrin, [a] benzoporphyrin, [a] benzoporphyrin derivative, [a] hematoporphyrin, or [a] hematoporphyrin derivative.
40. (Amended) The method of claim 33, wherein the method ameliorates the symptoms of [a disorder selected from the group consisting of] age-related macular degeneration[, ocular histoplasmosis syndrome, pathologic myopia, angioid streaks, idiopathic disorders, choroiditis, choroidal rupture, overlying choroid nevi, and inflammatory diseases].
41. (Amended) A method of treating unwanted choroidal neovasculature comprising endothelial cells in a mammal, the method comprising the steps of:

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- (a) administering to the mammal an anti-angiogenesis factor selected from the group consisting of angiostatin and an anti-vascular endothelial growth factor antibody in an amount sufficient to permit an effective amount to localize in the choroidal neovasculature;
- (b) administering to the mammal after step (a) an amount of a tetrapyrrole derivative photosensitizer sufficient to permit an effective amount to localize in the choroidal neovasculature; and
- (c) irradiating the choroidal neovasculature with laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal neovasculature, wherin damage to the endothelial cells resulting from the combination of steps (a), (b), and (c) is greater than that resulting only from the sum of steps (a), (b) and (c).

45. (Amended) The method of claim [44] 41, wherein the photosensitizer is lutetium texaphyrin, [a] benzoporphyrin, [a] benzoporphyrin derivative, [a] hematoporphyrin, or [a] hematoporphyrin derivative.

49. (Amended) The method of claim 41, wherein the method ameliorates the symptoms of [~~a disorder selected from the group consisting of~~] age-related macular degeneration[,-ocular histoplasmosis syndrome, pathologic myopia, angioid streaks, idiopathic disorders, choroiditis, choroidal rupture, overlying choroid nevi, and inflammatory diseases].